MIR Trial: Mirtazapine for treatment resistant depression in primary care

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List of abbreviations

Acronym	Details
A&E	Accident & emergency
AE	Adverse event
ASEC	Antidepressant Side-Effect Checklist
AUDIT-PC	Alcohol Use Disorders Identification Test Primary Care
BDI-II	Beck Depression Inventory (2nd version)
BNF	British National Formulary
CACE	Complier average causal effect
CI	Confidence interval
CIS-R	Clinical Interview Schedule – Revised version
CoBalT	Cognitive behavioural therapy as an adjunct to pharmacotherapy for primary care patients with treatment resistant depression: a randomised controlled trial
CRF	Case report form
DH	Department of Health
DMC	Data monitoring committee
EQ-5D-5L	EuroQol 5-dimension 5-level
GAD-7	Generalized Anxiety Disorder & Questionnaire
ICD-10	International Statistical Classification of Diseases and Related Health Problems (10th version)
IQR	Inter-quartile range
ITT	Intention to treat
MAOI	Mono-amine oxidate inhibitor
NHS	National Health Service
OP	Out-patient
PHQ9	Patient Health Questionnaire - 9
RCT	Randomised controlled trial
RL	Related to treatment
SAE	Serious adverse event (subset of AE)
SAP	Statistical analysis plan
SD	Standard deviation
SF-12	Short form 12
SNRI	Serotonin–norepinephrine reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitor
SUSAR	Suspected unexpected serious adverse reaction
TRD	Treatment resistant depression
UR	Un-related to treatment

1. INTRODUCTION TO SAP

1.1 Scope

This document details the approach that will be followed when analysing and reporting the results from the MIR trial.

The purpose of the plan is to:

1. Record the intended analyses in advance so as to ensure transparency of timing of any subsequent evolutions
2. Ensure that the analysis is appropriate for the aims of the trial and reflects good statistical practice in general
3. Explain in detail how the data will be handled and analysed to enable others to perform the actual analysis in the event of sickness or other absence
4. Protect the project by helping it keep to timelines and within scope

As well as outlining the statistical analyses of the clinical outcomes in this study, this SAP also provides a brief description of the proposed economic and qualitative evaluations that will be conducted by other members of the research team.

Additional exploratory or auxiliary analyses of data not specified in the protocol are permitted, but fall outside the scope of this analysis plan although such analyses would be expected to follow good statistical practice.

The analysis strategy will be made available if required by journal editors or referees when the main papers are submitted for publication. Additional analyses suggested by reviewers and editors will, if considered appropriate, be performed in accordance with the Analysis Plan, but if reported the source of such a post-hoc analysis will be declared.

1.2 Editorial changes

Any changes made to the analyses detailed in this SAP after approval will be clearly justified and documented as an amendment at the end of this document. The SAP will then be re-approved.

1.3 SAP document approval

The SAP will be authorised by Dr David Kessler (chief investigator), Prof Tim Peters and Clare Rutterford (DMC statistical reviewer).

1.4 Skeleton tables and figures

Throughout this document references are made to any skeleton tables and figures to be used in the reporting of the study (e.g. **Figure F1** or **Table T1**). Such tables and figures can be found in **Appendix A** of this document, and are intended as a guide for trial reporting. Final versions of the tables/figures may differ: tables may be combined, and/or their layout or numbering may evolve. However the content will be consistent with **Appendix A.**

2. STUDY BACKGROUND AND OBJECTIVES

2.1 Study background

Depression is common in primary care and antidepressants are widely prescribed, but many depressed people do not respond to treatment. Such treatment resistant depression (TRD) has considerable impact on individuals, health services and society. Results from the recently completed CoBalT study – a trial of the addition of cognitive behavioural therapy to antidepressants in the same group of treatment-resistant patients – were promising (1) but a substantial number of those treated remain depressed and we need to develop other treatment strategies.

There is a rationale for adding a second antidepressant with a different and complementary mode of action to selective serotonin reuptake inhibitor (SSRI) or serotonin–norepinephrine reuptake inhibitors (SNRI). Mirtazapine, a presynaptic alpha2-adrenoreceptor antagonist, increases central noradrenergic and serotonergic neurotransmission. Thus, there is the potential for a synergistic action and this could enhance clinical response compared to those only receiving an SSRI or SNRI.

MIR is a parallel group, double-blind multi-centre randomised controlled trial (RCT) where patients are allocated to either usual care or usual care plus mirtazapine (intervention). It is designed to assess the effectiveness of mirtazapine when given in addition to antidepressants in reducing depressive symptoms and improving quality of life over 12 months in patients with treatment resistant depression (TRD) in primary care.

2.2 Study objectives

The objective of this study is to investigate in adults of 18 years and over in primary care with TRD whether the use of mirtazapine, compared with placebo, reduces the symptoms of depression measured as a continuous variable at 12 weeks using the Beck Depression Inventory, second version (BDI-II) (2). This study will also describe a binary variable using the BDI-II, representing response, defined as a reduction in depressive symptoms of at least 50% compared to baseline, a widely used definition of improvement.

In relation to the use of mirtazapine compared with placebo, the study will also:

1) Investigate the rate of remission of symptoms, defined as a score on the BDI-II of less than 10.

2) Investigate any change on a measure of generalized anxiety, the Generalized Anxiety Disorder & Questionnaire (GAD-7) (3)

3) Measure all of the above outcomes at 24 weeks and 12 months

4) Measure antidepressant use and adherence

5) Estimate the cost-effectiveness from the perspectives of the NHS, patients and society

6) Compare all adverse events including: any new symptoms or worsening of existing symptoms, re-consultations for a documented deterioration in illness and Serious Adverse Events (SAEs)

2.3 Primary outcome

The primary outcome of this study is:

1) Continuous BDI-II score at 12 weeks, adjusted in the analysis for baseline BDI-II score

2.4 Secondary outcomes

The secondary outcomes of this study are as follows, with adjustments in the analyses for baseline scores of the relevant measure whenever available:

1) Response to treatment, measured as an improvement of at least 50% in BDI-II score at 12 weeks compared to baseline

2) Remission of symptoms, defined as a score on the BDI-II of less than 10 at 12 weeks

3) Generalized anxiety as measured by the GAD-7 at 12 weeks

4) All of the above outcomes at 24 weeks and 12 months

5) Antidepressant use and adherence (using Morisky and additional questions) at 12 weeks, 24 weeks and 12 months

6) Quality of life using the EuroQol 5-dimension 5-level (EQ-5D-5L) (4) questionnaire and social and physical functioning using the Short Form 12 (SF-12) questionnaire at 12 weeks, 24 weeks and 12 months

7) Cost-effectiveness from the perspectives of the NHS, patients and society (using self-report questionnaires at 12 and 24 weeks, and at 12 months; and primary care practice data on consultations, services and prescriptions over the 12 month trial period)

8) Adverse events including: any new symptoms or worsening of existing symptoms, consultations for a documented deterioration in illness and Serious Adverse Events (self-reported, or from primary care notes review); adverse effects (using the Antidepressant Side Effect Checklist (ASEC) (5) at 12 weeks and 12 months)

2.5 Changes to the study objectives during the course of the trial

To be updated as necessary

3. STUDY POPULATION

The study population is all patients satisfying all of the following inclusion criteria:

- Adults (over 18 years) in primary care
- Depression treated with at least 6 weeks at recommended British National Formulary (BNF) doses of any of the following SSRI or SNRI antidepressants: fluoxetine, sertraline, citalopram, escitalopram, fluvoxamine, paroxetine, duloxetine or venlafaxine.
- Have adhered to their medication for at least 6 weeks. In order to operationalize our definition of treatment resistance, we will use the Morisky 4-item self-report measure of compliance (6) as adapted for the CoBalT trial (1). The Morisky measure provides a score ranging from 0 (at least 80% compliance) to 4. Given the relatively long half-life of antidepressant medication, individuals who have not missed more than one consecutive dose will not be excluded
- Scoring at least 14 on the BDI-II questionnaire

- A diagnosis of depression using the International Statistical Classification of Diseases and Related Health Problems (ICD-10) assessed using the Clinical Interview Schedule – Revised version (CIS-R)

Any of the following warrants exclusion from the study:

- Currently taking combined or augmented antidepressant treatment
- Currently having their medication managed by a psychiatrist
- Bipolar disorder
- Psychosis
- Alcohol/substance abuse/dependence
- Pregnancy, planning pregnancy, breast feeding
- Patients who are unable to complete the study questionnaires
- Past history of an adverse reaction to mirtazapine
- Current treatment with a mono-amine oxidase inhibitor including moclobemide
- Other medical contraindications to mirtazapine
- Dementia (formal diagnosis)

Our primary outcome is the BDI-II score as a continuous variable. NICE guideline panel for the first depression guideline (7) suggested that a clinically important difference in BDI-II corresponds to about 3 points (0.35 standard deviations) on the Hamilton Depression Rating Scale (HDRS) (8) for non-TRD patients and 2 points for those who are TRD. The equivalent difference to 3 HDRS points on the BDI-II total score would be 3-4 points (standard deviation: 10-12 in the CoBalT trial). With 200 participants in each group, we would have 91% power to detect a difference of 0.33 standard deviations at the two-sided 5% significance level. Allowing for 15% loss to follow-up at 12 weeks, we would need to recruit 472 patients in total.

A widely accepted measure of clinical effect in depression is whether there has been a 50% reduction in symptoms as measured using the BDI-II score (1). As this is a particularly important secondary outcome – and relevant example of a binary outcome - we sought to estimate the size of effect we could anticipate detecting. We estimated that with 200 patients in each group we would have 90% power to detect a differences between 30% and 46% response, or an odds ratio of 2, at a two--sided 5% significance level.

We therefore planned to recruit 120 patients from 24 general practices at each of the four centres (Bristol, Exeter, Manchester/Keele and Hull/York).

Recruitment trends over the study period will be summarised in **Figure F1** and characteristics of the different centres are summarised in **Table T1**.

3.1 Flow of participants

a) Recruitment

Primary care patients are recruited into the trial using a three stage approach to identify those satisfying our inclusion criteria. The system is described below and illustrated in a CONSORT diagram (**Figure F2**).

Stage 1: Record search to identify potentially eligible patients – those who have been prescribed SSRI or SNRI antidepressants for at least 6 weeks at an adequate dose	General Practices (GPs) will conduct a search of their computerised records for potentially eligible patients. These patients are then mailed an invitation by their GP asking for their permission to be contacted by the research team. Concurrent with this, GPs will identify patients in consultation that they think might be suitable for the trial. GPs will introduce the trial and ask the patient for their consent to be contacted by the research team.
Stage 2: Postal screening to measure depressive symptoms	Those patients consenting to be contacted by the research team are mailed a brief questionnaire asking about their depressive symptoms and use of medication to assess who might have TRD.
Stage 3: Baseline interview to assess eligibility	Those patients deemed eligible at the postal screening are invited to attend a baseline interview where a computerised questionnaire is completed to ensure that patients meet the eligibility criteria: BDI-II score of 14 or more, have been adherent to antidepressants for at least 6 weeks and who have an ICD-10 diagnosis of depression. Those who have met the eligibility criteria are invited to enter the trial.

b) Follow-up

Eligible participants who agree to participate will be followed for 12 months from baseline. The system is described below and illustrated in a separate CONSORT diagram (**Figure F3**).

Randomisation	Patients fulfilling the eligibility criteria in Stage 3 and consenting to participate in the trial will be randomised to receive usual care + placebo (comparator) or usual care + mirtazapine (intervention)
2 weeks	At 2 weeks post-baseline participants will be contacted by telephone to check that they have received and started their trial medication.
6 weeks	At 6 weeks the research associate will contact the participant and ask again about adherence, adverse events and ask participants to complete the BDI-II.
12 weeks	At 12 weeks the participants will complete the BDI-II as well as the Morisky, ASEC, Patient Health Questionnaire – 9 (PHQ9), GAD-7, EQ-5D-5L, Short form 12 (SF-12) and health economics questionnaires.
24 weeks	At 24 weeks the participants will complete the same questionnaires as at 12 weeks, but without the ASEC measure.

12 months	At 12 months the participants will complete the same questionnaires as at 12 weeks. In addition, participants will be asked to complete a short feedback questionnaire after their 12 month assessment.

A summary of the data collected at each time point is presented in **Appendix B**. A summary of the recruitment statistics at each centre will be presented in **Table T2**.

3.2 Characteristics of non-study patients

We will compare age and gender distributions between the following groups of patients:

1. Patients identified by GPs as potential participants *vs* those the GPs excluded via the record search (**Table T3**)

2. Patients who accepted the invitation to participate in the trial *vs* those who declined and those who did not respond (**Table T4**)

3. Patients who returned a completed screening questionnaire *vs* those who returned a blank questionnaire or no questionnaire (**Table T5**).

4. Patients who agreed to attend a baseline assessment with a researcher *vs* those who declined or did not respond (**Table T6**)

5. Patients who were found to be eligible to participate based on their baseline assessment (including those who declined to participate) *vs* those who were not eligible (**Table T7**).

We will also compare the distribution of socio-economic status collected in the postal screening questionnaire between those who agreed to attend a baseline assessment vs those who declined (**Table T8**) and make similar comparisons between those who were eligible to participate based on their baseline assessment (including those who declined to participate) with those who were not found to be eligible (**Table T9**).

3.3 Randomisation

We employed stratification by centre (n=4), with minimisation used to ensure balance in baseline BDI-II score (using approximate tertiles derived from the CoBalT baseline scores: <26, 26-34, ≥35), gender and whether the patient was currently receiving a psychological therapy. Minimisation with a probability weighting of 0.8 was used to reduce predictability. After an eligible patient consented to participate, their details were entered onto a secure, web-based data collection platform along with the patient ID number and a medicine ID number was allocated to them.

The University Hospital Bristol Pharmacy held the randomisation schedule and a log of which Medicine Pack was allocated to each patient (hereafter referred to as the code-break) and provide a 24-hour emergency un-blinding service.

A standardised procedure for breaking the code was available (UH Bristol Emergency Code Break Procedure, version CT 502). When necessary, the code for a particular patient could be broken at any moment during the trial. Before the 12 week primary outcome, the codes could only be broken in case of a medical emergency, if unblinding could influence the patient's treatment, or the patient has suffered an unexpected serious event. After the 12 week primary outcome, the code could be broken at the request of the participant or their GP. The code-break could only be related to the investigative team once written confirmation had been received

that primary outcome data analysis is complete. The UH Bristol Pharmacy would also record a list of all participants and their treatment allocation and file this in the pharmacy trial file and provide a copy to the Trial Manager at the end of the trial.

There were a small number of instances where errors occurred in the randomisation.

Error	Impact on randomisation	Action taken
Incorrect date of birth (n=3 patients)	As age was not included in the minimisation so has no impact on randomisation	Date of birth will be corrected in the analysis
Incorrect randomisation date inputted on administrative database (n=1 patient)	This was a recording issue after randomisation so has no impact on the randomisation itself	The administrative database was updated with the correct randomisation date
Incorrect centre (n=2)	Patients were mistakenly identified as being from the Bristol centre at randomisation. As we stratified on centre this means the	The error will be carried forward in the analysis. Analyses stratified by centre were not planned.

3.4 Protocol deviations

The following types of protocol deviation will be considered:

- Patient received the alternative treatment to that allocated prior to routine unblinding. Note that patients can be unblinded at 12 weeks and continue to be followed after that.
- Patient receiving usual care and neither placebo nor mirtazapine.
- Patient did not meet the study eligibility criteria but was entered into the study.

Note it may be possible for patients to be classified as a protocol deviation for more than one reason.

The frequency of each type of deviation will be tabulated by treatment allocation (**Table T10**) with full details given in separate listings (**Table T11**).

3.5 Withdrawals from the trial medication

During the study period the GP or other health care professional may decide to make changes to the participant's psychotropic drug regime, for example because of failure to respond. All participants will be taking an SSRI or SNRI antidepressant at entry to the study. If it is decided that it is advisable to change from one SSRI to another, or to swap an SSRI to an SNRI or vice versa, then there is no reason for the participant to withdraw from the trial medication. However, if the decision is to commence a mono-amine oxidase inhibitor (MAOI) then the participant should be withdrawn from the trial medication for 2 weeks before this is done. If

the participant's GP or another health professional decides that it is appropriate for the participant to commence another augmenting treatment, such as Lithium or an antipsychotic drug, then we would advise that they be withdrawn from the trial medication. We will include this advice on appropriate information sheets.

Although there is no evidence that the medication is teratogenic, if a patient discovers that she is pregnant during the trial, she will be instructed to stop her trial medications immediately, though she will be able to continue to participate in completion of the trial outcome measures if she wishes. A longer monitoring period will be put in place to establish the safe delivery of a healthy infant, at which point follow-up will stop.

We anticipate that a proportion of participants who request un-blinding at 12 weeks will have benefitted from the addition of mirtazapine to their treatment and will wish to continue this treatment. Likewise, some of those who have been in the placebo arm of the study, when un-blinded, may wish to try treatment with mirtazapine. Further prescribing of trial medication will not be available once participants are un-blinded and would be at the discretion of the GP. We will continue to prescribe trial medications for those who decide to remain blinded.

Participants are of course free to withdraw from the trial medication at any time for any reason without their medical care being affected. Where possible, data already collected will continue to be used in the trial and patients who withdraw from the trial medication will be asked if they are willing to provide follow-up data as part of our intention to treat (ITT) analysis, see **section 3.6**.

If a patient withdraws, the reason for and type of withdrawal will be documented in the Case Report Form (CRF). Principal Investigators have the right to withdraw patients from the trial drug in the event of inter-current illness, Adverse Events (AEs), Serious Adverse Events (SAEs), Suspected Unexpected Serious Adverse Reactions (SUSARs), protocol violations, administrative reasons or other reasons; this will be documented in the CRF. Data on all withdrawals from the trial medication will be tabulated by treatment allocation (**Table T12**) with full details given in separate listings (**Table T13**).

3.6 Analysis sample

Analysis and reporting will be in line with CONSORT guidelines with the primary analyses being conducted on an intention to treat ('ITT') basis using complete cases.This differs subtlety from a true ITT analysis which would use imputation or other methods of addressing missing data to ensure that all randomized patients are included in the final analysis.

Per protocol analyses at 12 weeks and 12 months will be based on those who have remained on their intended study medication at that point. Since these analyses are likely to be biased, however, we will also use the Complier Average Causal Effect (CACE) approach as described in **section 5.2.5.2**. Sensitivity analyses using the CACE approach will also be conducted at 24 weeks as described in **section 5.2.5.2**.

3.7 Safety sample

In a safety analysis the safety sample in this study includes all randomised patients. Data will be analysed according to the treatment received and we will use descriptive statistics to describe serious adverse events in both groups.

4. DERIVATIONS

4.1 Primary outcome

The primary outcome in this study relates to the patient's BDI-II score at 12 weeks.

4.2 Secondary outcomes

- **Response in depression symptoms** is a binary variable defined as a reduction in the BDI-II of at least 50% at 12 weeks as compared to baseline. This will also assessed at 24 weeks and 12 months adjusting for baseline.

- **Remission of depression symptoms** is derived from the BDI-II score and is classified as having occurred if the score is less than 10 and not occurred if 10 or greater. It will be derived at 12 and 24 weeks and 12 months.

- **Anxiety symptoms** is derived from the GAD-7 score which will be calculated using standard formulae. It will be derived at 12 and 24 weeks and 12 months adjusting for baseline GAD-7 score.

- **Adherence to antidepressants** at 12 weeks is assessed using information on patient-reported breaks in treatment and the Morisky questionnaire. Patients were considered adherent or non-adherent based on the definitions described below:

Non-adherent	Non-adherent patients will have not started treatment or started less than 6 weeks prior. For those having started treatment at least 6 weeks prior, we will examine patients' Morisky scores based on treatment in the last 6 weeks. Patients will be deemed non-adherent in any of these scenarios: 1. they have a score of 1 and missed 2 or more days in a row of their study medication 2. they have a score of 2 based on forgetting to take and were careless at times about taking their study medication and missed 2 or more days in a row of their study medication 3. they have a score of 2 and reported stopping treatment when feeling better or worse 4. they have a score of >2.
Adherent	Adherent patients will have started treatment at least 6 weeks earlier and their Morisky score fulfils one of the following scenarios: 1. they have a score of 0 2. they have a score of 1 and did not miss more than 2 days in a row of their study medication 3. they have a score of 2 based on forgetting to take their study medication and being careless at times about taking their study medication, but

	reported not missing 2 or more consecutive days of their study medication in the last 6 weeks.

There is no established clinical guidance on defining adherence to mirtazapine. The 6-week threshold for starting treatment was therefore chosen as being clinically sensible, but we will explore the distribution of the data to assess whether a 7 or 8-week cut-off would be more appropriate. Once we will have decided the most appropriate cut-off we will perform the more involved analyses described in **section 5**.

- **Quality of life** is measured using the EQ-5D-5L questionnaire – a standardised measure of health status measured at 12 and 24 weeks and 12 months. Scores were calculated using standard algorithms, with higher scores indicating better health.

- We will use the ASEC measure of antidepressant side effects to assess whether the patient reported **adverse effects** related to their trial medication. This is assessed at baseline, 12 weeks and at 12 months. At each of these time points, patients are provided with a list of 21 symptoms and are asked to report on a scale of 0 (absent) to 3 (severe) the severity of these symptoms. Patients are also asked, for each symptom, whether they felt the symptom was likely to be related to their usual antidepressant medication (baseline) or the trial medication (12 weeks and 21 months). A total score is obtained by taking the sum of the severity scores across all 21 items and is treated as a continuous measure.

  We will document all **Serious Adverse Events** and **Adverse Events** (as described in **section 5.3**) by 12 months. Each adverse event will be rated by at least one clinician as to its relatedness to the study medication and we will present descriptive statistics by trial arm and by relatedness to the study medication We will report the number of events per person and categorise these according to the distribution of the counts.

- The **cost-effectiveness** from the perspectives of the NHS, patients and society (including information on the use primary and community care services, prescriptions issued, secondary care, social services and disability payments, personal costs and time off work and unpaid activities) form part of the economic analyses described in **Appendix C**.

5. DATA VALIDATION

Prior to any data analyses, a random selection of 10% of patients will be identified by the trial manager and all of their questionnaires verified to ensure that the database reflected the information reported on the questionnaire. Given the importance of the BDI-II response at 12 weeks, a further 10% of patients will be identified by the trial manager and their BDI-II responses on the 12 week questionnaire (as reported on the database) will be verified against the hard-copy questionnaires. Where any errors are found, these will be amended on the database. If we observe data entry errors in more than a negligible proportion of the total number of data fields verified we will increase the number of questionnaires verified and check all BDI-II responses at 12 weeks.

Once these verifications are performed, internal consistency checks will be performed to identify spurious values or inconsistencies in responses. When inconsistencies are identified, these are reported to the trial manager who verifies the completed CRFs.

6. STATISTICAL ANALYSES

The primary analyses described in this section are highly specified therefore the statistician conducting these will not be blinded. Secondary analyses require unblinding in order to be informative. As the health economic analyses are less highly specified, however, the researcher conducting these will be blinded.

6.1 Baseline data

Baseline characteristics will be described by treatment group for patients in the analysis population (**Table T14**). The following variables will be considered:

Stratification variable:	Centre
Minimisation variables:	Gender Baseline BDI-II score Current receipt of psychological services
Socio-demographic variables:	Age Ethnic group Marital status Employment status Educational attainment Housing Financial well-being Alcohol consumption (AUDIT-PC score) Number of life events in the past 6 months Social support score Long-standing illness Caring responsibilities
Treatment preference	Preference for one treatment group over the other
Measures of depression	Suffered depression in the past Family history of depression Previous psychiatric referral Number of prior episodes of depression Length of current course of antidepressants ICD-10 primary diagnosis Secondary psychiatric diagnosis according to the CIS-R Depression severity: BDI-II score Generalised anxiety: GAD-7 score Depression severity: PHQ9 score Quality of life: EQ-5D-5L Health status: SF-12 mental subscale Health status: SF-12 physical subscale CIS-R Suicidal ideation

Continuous variables will be summarised using the mean and standard deviation (SD) (or median and inter quartile range (IQR) if the distribution is skewed), and categorical data will be summarised as a number and percentage. The summary statistic headings given in **Tables T14** are those we expect to use based on a-priori knowledge of the clinical measurements gained from previous studies. However, if distributional assumptions are not valid, changes will be made. Similarly, categories will be collapsed if the numbers of patients in groups are too few and groups may be alternatively combined.

We will also describe all antidepressant medication use at baseline reporting the class, name, dose and duration of treatment. These data are summarised in **Table T15**.

Stratification, minimisation and socio-demographic variables and measures of depression and treatment preference assessed at baseline which are associated with "missingness" of the primary outcome measure – BDI-II score - within the dataset at all follow-up points (12 weeks, **Table T16**; 24 weeks, **Table T17**; 12 months, **Table T18**) will be explored and described. Comparisons will be made using a chi-square test for categorical baseline variables and t-tests or Mann-Whitney tests for continuous data.

6.2 Primary and secondary outcome data

6.2.1 Adjustment in models

The primary analysis will be of the BDI-II score at 12 weeks post-randomisation, measured as a continuous variable. A linear regression model will be used to compare the groups as randomised and will adjust for stratification and minimisation variables and baseline measurements of the outcome. Secondary analyses of this outcome will also include adjustment for any prognostic variables demonstrating marked imbalance at baseline (ascertained using descriptive statistics).

Analyses of secondary outcomes will be conducted adjusting for the baseline measure of the outcome variable, stratification and minimisation variables together with (in further regression models) additional adjustment for any variables that show imbalance at baseline.

6.2.2 Analysis models

Linear regression models will be used for continuous outcomes and logistic regression models for binary outcomes. For all treatment comparisons the usual care + placebo (comparator) group will be the reference group. Adjustment for any baseline imbalance will be performed as described in **section 6.2.1**. All outcomes listed in the study protocol will be presented as per the template tables **Table T19** to **T26**.

We will also use repeated measures analyses incorporating the outcome at 12 and 24 weeks and 12 months post-randomisation to examine whether any treatment effects are sustained, diminished or emerge later. This will be investigated formally by the introduction of an interaction between treatment group and time.

In all analyses we will present regression coefficients (or odds ratios for binary outcomes), with 95% confidence intervals and p-values from likelihood ratio tests.

6.2.3 Model assumptions

For all methods outlined underlying assumptions will be checked using standard methods. If assumptions are not valid then alternative methods of analysis will be sought.

6.2.4 Subgroup analyses

We will conduct pre-planned subgroup analyses to investigate any differential effects according to a number of factors. These will be done by introducing appropriate interaction terms in the regression models. We will carry out these analyses by baseline depression severity (BDI-II) and a five-level measure of the degree of treatment resistance based on duration of symptoms and prior treatment with antidepressants.

6.2.5 Sensitivity analyses

5.2.5.1. Missing data

In all tables missing data will be indicated by footnotes. If the amount of missing data differs substantially between treatment groups potential reasons will be explored. Sensitivity analyses will be conducted (including the use of multiple imputation methods) to examine the influence of missing data on the key trial findings.

For our repeated measures analyses incorporating outcomes over time, we will investigate the influence of missing data using sensitivity analyses that make different assumptions, such as "best" and "worst" case scenarios, as well as using multiple imputation by chained equation (MICE) to impute missing data where assumptions are met. When using MICE, 25 datasets will be generated and 10 switching procedures undertaken. The imputation model will include all variables predictive of missingness, together with all of the variables included in the main substantive model. Comparisons of results from ITT analyses of complete cases with ITT analyses where missing data were imputed are presented in **Table T27**. MICE assumes that the missing data are missing at random and we will examine the sensitivity of our results to departures from this assumption.

5.2.5.2. Per protocol and CACE analyses

We propose to carry out per protocol analyses at 12 weeks and 12 months. These will only compare individuals who have remained on the trial medication at that follow-up point. Since these analyses are likely to be biased, we will also use the Complier Average Causal Effect (CACE) approach. This provides an unbiased estimate for the treatment effect for those who have complied with the active treatment. "Compliers" will be identified based on the dichotomous adherence variable defined in **section 4.2.** This approach would be justified if the characteristics of those who adhered to the comparator treatment differed from those that adhered to usual treatment + mirtazapine. This is plausible as we would expect intolerance of the side effects to be more important for the mirtazapine group and non-response to be more of an issue for the comparator group. If there is differential adherence in the two arms we will also investigate structural mean approaches as described by Fisher *et al* (9) and, separately, use extensions of CACE as described by White *et al* (10).

At 12 and 24 weeks and 12 months, the ITT analysis will compare the randomised groups. By these stages, we would still expect any of those who had responded to mirtazapine to remain on the combination treatment. The ITT analyses will therefore provide an estimate of any longer term benefit attributed to the early response to mirtazapine with an SSRI/SNRI. The interpretation of this will depend upon whether other potentially active interventions are balanced between the groups. If we do find that the groups differ markedly in the two arms we will investigate any possible impact of this by adjustment for the other interventions in the regression model.

A further sensitivity analysis using CACE methods could be used at 24 weeks and 12 months. "Compliers" will be identified based on the dichotomous adherence variable defined in **section 4.2**. After defining "compliers" in this manner we can then estimate the effect of completing a 12 week course of mirtazapine on depression outcomes at the later follow-up points (24 weeks and 12 months).

Results from all of these analyses will be presented as in **Tables T28-T36**.

5.2.5.3. Timing of questionnaire completion

We record the dates of completion of questionnaires at different time points allowing us to calculate the time since baseline at which they were completed. Using descriptive statistics and appropriate comparative tests (such as Mann-Whitney, two-sample t-tests or regression models), we will assess whether there is evidence of any differences between treatment groups in terms of the time since baseline at which a questionnaire was completed. Should there be any suggestion of meaningful differences between groups then we will perform additional secondary analyses adjusting for timing of completion of the relevant questionnaire(s).

6.2.6 Multiple testing

No formal adjustment will be made for multiple testing. Consideration will be taken in interpretation of results to reflect the number of statistical tests performed and the consistency, magnitude and direction of treatment estimates for different (secondary) outcomes.

6.3 Safety data

Adverse events (AEs) are defined as any untoward medical occurrence in a clinical trial participant. An AE does not necessarily have to have a causal relationship with the trial treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal finding), symptom or disease temporally associated with the use a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (International Conference on Harmonisation (ICH) definition). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities. All AEs will be recorded in the Case Report Form (CRF) for the duration of the participant's direct involvement in the trial (12 months).

A serious adverse event (SAE) is defined by ICH as any untoward medical occurrence that at any dose of the trial medication meets any of the following conditions:

(i) **Results in the death of the participant**

(ii) **Is life-threatening**. The term "life-threatening" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

(iii) **Requires inpatient hospitalisation or prolongation of existing hospitalisation**. For any event that may jeopardise the participant or may require intervention to prevent one of these outcomes, the CI should exercise his/her scientific and medical judgement to decide whether or not such an event requires expedited reporting to UH Bristol

(iv) **Results in persistent or significant disability/incapacity**. Any event that seriously disrupts the ability of the participant to lead a normal life, in other words leads to a persistent or permanent significant change, deterioration, injury or perturbation of the participant's body functions or structure, physical activity and/or quality of life.

(v) **Is a congenital anomaly/birth defect**. Exposure to the trial drug before conception (in men or women) or during pregnancy that resulted in an adverse outcome in the child

(vi) **Other medical events**. Medicinal events that may jeopardise the subject or may require an intervention to prevent a characteristic or consequence of a SAE. Such events are referred to as "important medical events" and are also considered as "serious" in accordance with the definition of a SAE.

An AE is considered to be associated with the use of the drug if the attribution is possible, probable or very likely by the definitions listed below:

(i) **Not likely**. An AE that is not related to the drug

(ii) **Unlikely to be related**. An AE for which an alternative explanation is more likely (e.g. concomitant drug(s), concomitant disease(s) or the relationship in time suggests that a causal relationship is unlikely.

(iii) **Possibly related**. An AE that might be due to the use of the drug and for which an alternative explanation, e.g. concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable and therefore, the causal relationship cannot be excluded.

(iv) **Probably related**. An AE that might be due to the use of the drug. The relationship in time is suggestive (e.g., confirmed by IMP withdrawal). An alternative explanation is less likely, e.g. concomitant drug(s), concomitant disease(s)

(v) **Definitely related**. An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g. concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g. it is confirmed by IMP withdrawal and re-introduction)

AEs occurring in the study period for all patients in the safety population will be tabulated as per **Table T37 to T39**. All events will be presented grouped by the treatment received, rather than the treatment allocated.

Table T37 summarises expected adverse events listed in the study protocol, with events that meet the serious criteria as outlined above indicated. Such events are captured via the study CRFs. They are grouped according to the disease system affected. Additionally, expected adverse events were stratified by treatment group and relatedness to the study treatment (**Table T38**).

Table T39 summarises unexpected serious adverse events (SAEs) – that is events that are not listed in the study protocol that meet the SAE criteria. Such events are captured via separate SAE report forms and full details will also be given as listings, with events that are classified as possibly, probably or definitely related highlighted (see **Table T40**).

Table T41 summarises the number of adverse events (including SAEs) reported per patient stratified by relatedness to treatment.

No formal comparisons between treatment groups will be made, as numbers of events are expected to be small.

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8. AMENDMENTS TO THE SAP

Previous version	Previous date	New version	New date	Brief summary of changes

APPENDIX A: SKELETON TABLES AND FIGURES

Section	Outputs	
Section 1 Population	**Tables, figures and listings detailing the study population**	
	Figure F1	Predicted and actual recruitment
	Table T1	Practice details by centre
	Figure F2	Flow of participants: recruitment pathway
	Figure F3	Flow of participants: randomisation onwards
	Table T2	Recruitment statistics by centre
	Table T3	Comparison of age and gender of those identified by GPs as potential participants and those who were excluded based on the record search
	Table T4	Comparison of age and gender of those accepting the invitation to participate in the trial with those who declined and those who did not respond
	Table T5	Comparison of age and gender of those completing the screening questionnaire and those who did not complete the screening (not returning a questionnaire or returning a blank questionnaire)
	Table T6	Comparison of age and gender of those completing the baseline assessment and those declining to attend or not responding
	Table T7	Comparison of age and gender of those eligible to participate based on their baseline assessment with those who were not eligible
	Table T8	Comparison of socio-economic status of those who did and did not agree to attend a baseline assessment
	Table T9	Comparison of socio-economic status of those who were eligible and not eligible at baseline
	Table T10	Protocol deviations
	Table T11	Details of individual protocol deviations
	Table T12	Withdrawals from the trial medication
	Table T13	Details of individual withdrawals from the trial medication
Section 2 Baseline data	**Summary tables of demographic information**	
	Table T14	Baseline comparability of randomised groups
	Table T15	Antidepressant medication use at baseline
	Table T16	Summary of baseline variables related to missing BDI-II at 12 weeks
	Table T17	Summary of baseline variables related to missing BDI-II at 24 weeks
	Table T18	Summary of baseline variables related to missing BDI-II data at 12 months
Section 3 Outcomes	**Summary data and treatment estimates**	
	Table T19	Primary outcome: mean and difference in mean BDI-II scores at 12 weeks
	Table T20	Means and differences in mean BDI-II scores at 24 weeks and 12 months
	Table T21	Percentage and OR of "response to treatment" (improvement of at least 50% in BDI-II score compared with baseline) at 12 weeks, 24 weeks and 12 months
	Table T22	Percentage and OR of "remission of symptoms" (BDI-II of less than 10) at 12 weeks, 24 weeks and 12 months

Section	Outputs	
	Table T23	Means and differences in mean GAD-7 scores at 12 weeks, 24 weeks and 12 months
	Table T24	Percentage and OR of adherence at 12 weeks
	Table T25	Means and differences in mean EQ-5D-5L scores at 12 weeks, 24 weeks and 12 months
	Table T26	Means and differences in mean ASEC scores at 12 weeks and 12 months
	Table T27	Comparison of results of ITT analysis of complete cases with ITT analysis where missing data were imputed using "best" and "worst" case scenarios and multiple imputation for primary outcome of BDI-II score at 12 weeks
	Table T28	Comparison of results from ITT, per protocol and CACE analyses for the primary outcome of BDI-II score at 12 weeks
	Table T29	Comparison of results from ITT and CACE analyses for the outcome of BDI-II score at 24 weeks
	Table T30	Comparison of results from ITT, per protocol and CACE analyses for the outcome of BDI-II score at 12 months
	Table T31	Comparison of results from ITT and CACE analyses for the outcome of improvement of at least 50% in BDI-II score at 12 weeks compared with baseline
	Table T32	Comparison of results from ITT and CACE analyses for the outcome of improvement of at least 50% in BDI-II score at 24 weeks compared with baseline
	Table T33	Comparison of results from ITT and CACE analyses for the outcome of improvement of at least 50% in BDI-II score at 12 months compared with baseline
	Table T34	Comparison of results from ITT and CACE analyses for the outcome of remission of symptoms defined by a BDI-II score of less than 10 at 12 weeks
	Table T35	Comparison of results from ITT and CACE analyses for the outcome of remission of symptoms defined by a BDI-II score of less than 10 at 24 weeks
	Table T36	Comparison of results from ITT and CACE analyses for the outcome of remission of symptoms defined by a BDI-II score of less than 10 at 12 months
Section 4 Safety data	**Summary tables and listings of all adverse events and serious adverse events**	
	Table T37	Expected adverse events and serious adverse events
	Table T38	Expected adverse events and serious adverse events by relatedness of treatment (UR: un-related; RL: related)
	Table T39	Unexpected adverse events and serious adverse events
	Table T40	Details of serious unexpected adverse events
	Table T41	Number of adverse events per patient stratified by relatedness to treatment

A1: Population

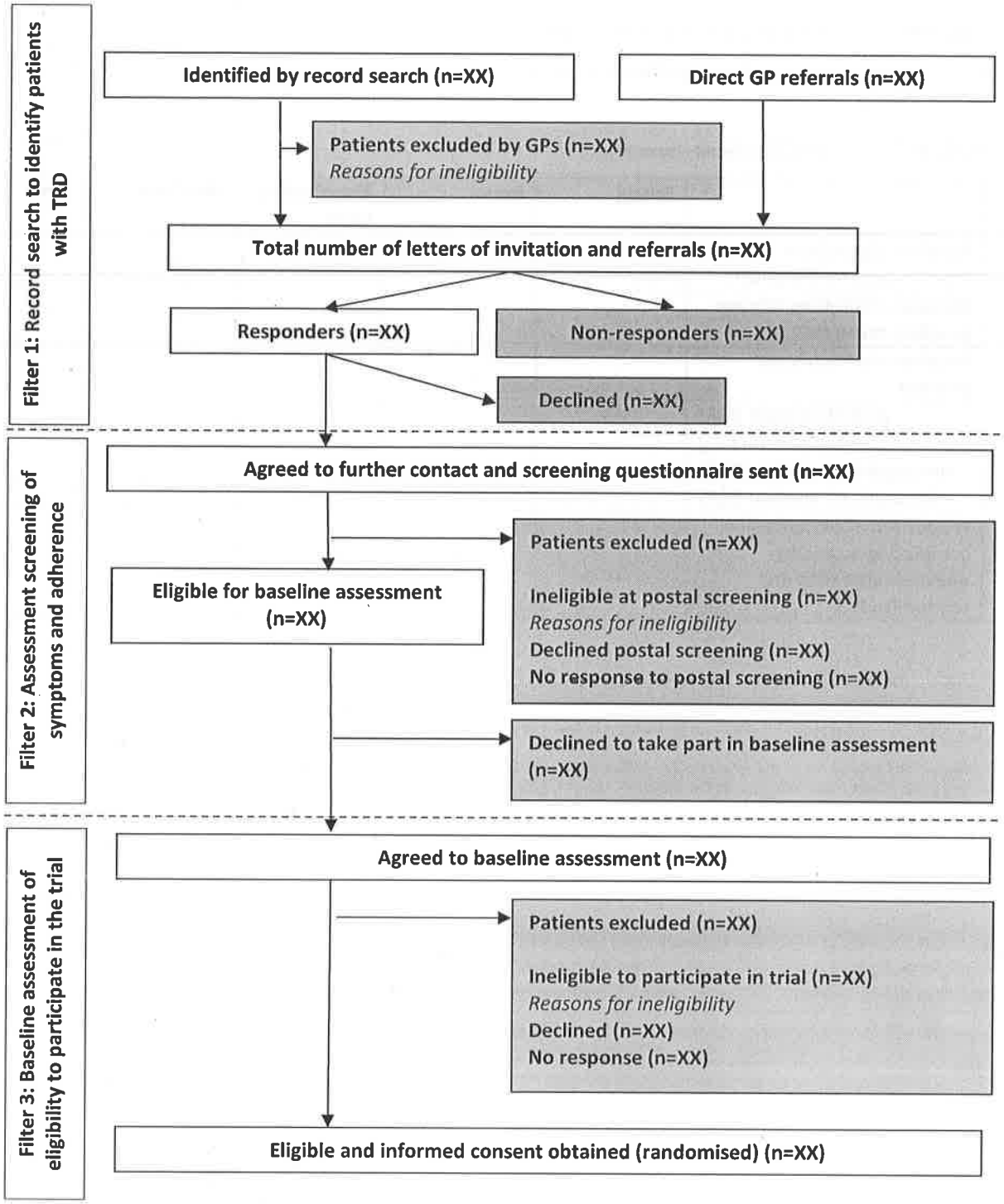
Figure F1 Predicted and actual recruitment

X axis: Month; Y axis: Number of patients recruited

Table T1 Practice details by centre

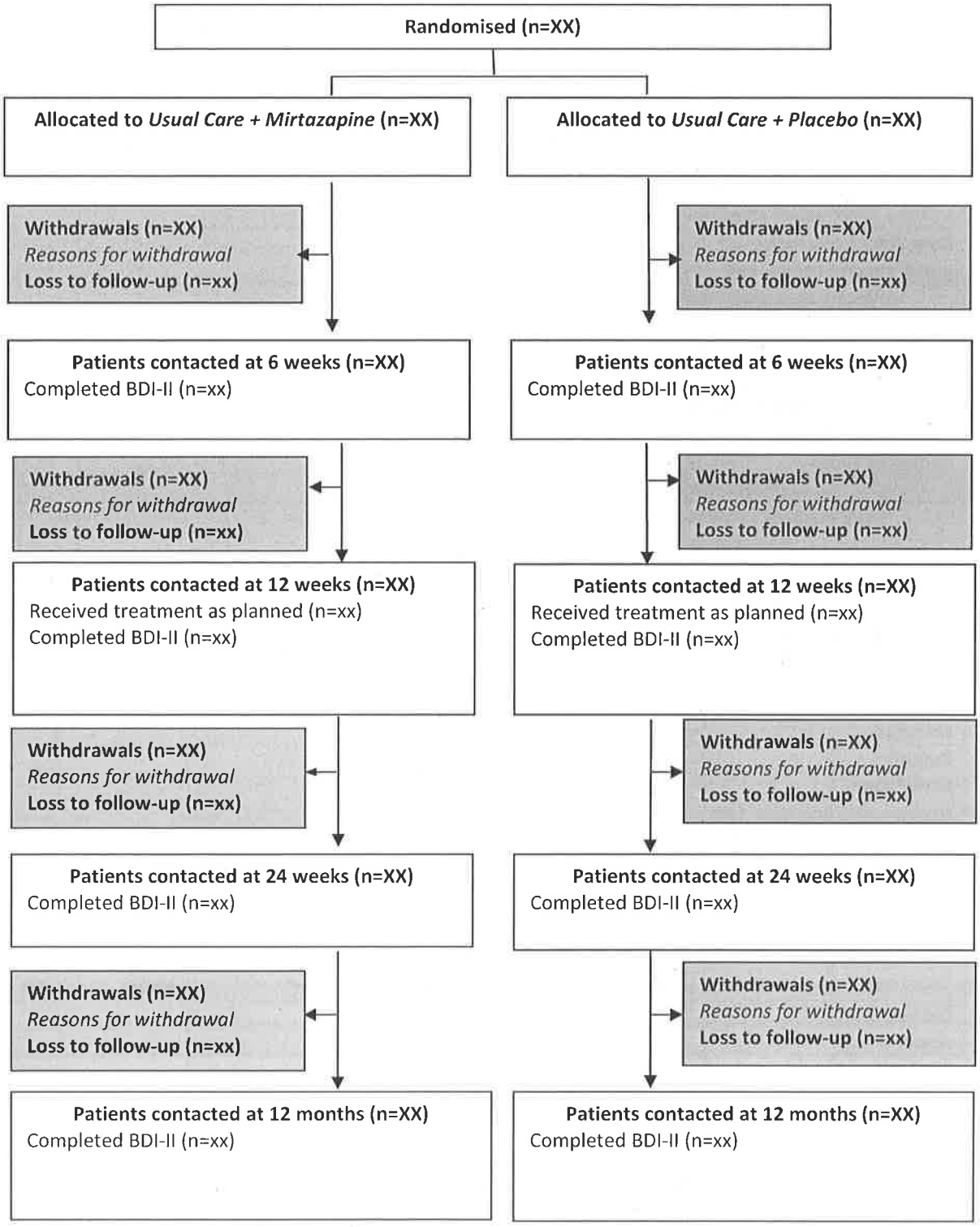
	Bristol	Exeter	Manchester/ Keele	Hull/York	Total
Number of practices					
Practice size: median (IQR)					
Number of full-time GPs per practice: mean (SD)					
Number of patients per practice					
Invited: median (IQR)					
Completed screening questionnaire: median (IQR)					
Randomised: median (IQR)					
Proportion of patients completing screening questionnaire who are randomised: %					

Figure F2 **Flow of participants: recruitment pathway**



Notes:
Some patients may be ineligible for more than one reason

Figure F3 **Flow of participants: randomisation onwards**



Notes:
Some patients may be ineligible for more than one reason
Patients are deemed to have received treatment as planned at 12 weeks if they fulfil the adherence criteria as defined in ***Section 4.2.***

Table T2 Recruitment statistics by centre

	Bristol	Exeter	Manchester/ Keele	Hull/York	Total
Number of practices					
Invitations/GP referrals					
GP referrals					
Total invitations					
Number returned					
Number accepted					
Percentage accepted					
Assessment screening questionnaire completed					
Percentage completed assessment screening					
Eligible for baseline assessment					
Percentage eligible					
Baseline assessments					
Randomisations					
Number					
Percentage of baseline assessments					

Table T3 Comparison of age and gender of those identified by GPs as potential participants and those who were excluded based on the record search

		Age			Female		
	N	n[a]	Mean	SD	n[a]	Mean	SD
Excluded							
Potential participant							

[a] *Number with available data*

Table T4 Comparison of age and gender of those accepting the invitation to participate in the trial with those who declined and those who did not respond

		Age			Female		
	N	n[a]	Mean	SD	n[a]	Mean	SD
Did not respond							
Declined							
Accepted							

[a] *Number with available data*

Table T5 Comparison of age and gender of those completing the screening questionnaire and those who did not complete the screening (not returning a questionnaire or returning a blank questionnaire)

		Age			Female		
	N	n[a]	Mean	SD	n[a]	Mean	SD

Did not complete screening							
Completed screening assessment							

[a] *Number with available data*

Table T6 Comparison of age and gender of those completing the baseline assessment and those declining to attend or not responding

		Age			Female		
	N	**n[a]**	**Mean**	**SD**	**n[a]**	**Mean**	**SD**
No (declined or not responding)							
Yes (agreed)							

[a] *Number with available data*

Table T7 Comparison of age and gender of those eligible to participate based on their baseline assessment with those who were not eligible

		Age			Female		
	N	**n[a]**	**Mean**	**SD**	**n[a]**	**Mean**	**SD**
Ineligible at baseline							
Eligible (including declined to participate)							

[a] *Number with available data*

Table T8 Comparison of socio-economic status of those who did and did not agree to attend a baseline assessment

	No (declined)	**Yes (agreed)**
Employment status **N** **n[a]**		
In paid employment (full/part-time); n (%)		
Not in employment; n (%)		
Unemployed owing to ill health; n (%)		
Educational attainment **N** **n[a]**		
A-level, higher grade or above; n (%)		
GCSE, standard grade or above; n (%)		
No formal qualifications; n (%)		
Housing **N**		

n[a]		
Home owner; n (%)		
Tenant or living with relative/friend; n (%)		
Hostel/care home, homeless or other; n (%)		

[a] *Number with available data*

Table T9 Comparison of socio-economic status of those who were eligible and not eligible at baseline

	Ineligible at baseline	Eligible (including declined to participate)
Employment status N n[a]		
In paid employment (full/part-time); n (%)		
Not in employment; n (%)		
Unemployed owing to ill health; n (%)		
Educational attainment N n[a]		
A-level, higher grade or above; n (%)		
GCSE, standard grade or above; n (%)		
No formal qualifications; n (%)		
Housing N n[a]		
Home owner; n (%)		
Tenant or living with relative/friend; n (%)		
Hostel/care home, homeless or other; n (%)		

[a] *Number with available data*

Table T10 Protocol deviations

	Randomised to Usual care + mirtazapine (n=)		Randomised to Usual care + placebo (n=)		Overall (n=)	
	Patients	%	Patients	%	Patients	%
Any protocol deviation						
Patient received the alternative treatment to that allocated prior to routine unblinding						
Patient received usual care and neither placebo nor mirtazapine						
Patient did not meet the study eligibility criteria but was entered into the study						
.....						

Table T11 Details of individual protocol deviations

Allocated treatment group	Centre	Further details (exact nature dependent upon type of deviation)
...		

Table T12 Withdrawal from the trial medication

	Randomised to Usual care + mirtazapine (n=XX)		Randomised to Usual care + placebo (n=XX)		Overall (N=XX)	
	n	%	n	%	n	%
Any withdrawal from the trial medication						
Reason						
I felt better						
The tablets caused side-effects						
My doctor and I agreed to stop my tablets						
I was afraid of becoming addicted						
The tablets made me feel worse						
The tablets were not making me feel better						
I prefer to take just 1 antidepressant						
I want to try other treatments						
Other						
.. details						

Table T13 Details of individual withdrawals from the trial medication

Allocated treatment group	Days between randomisation and withdrawal from the trial medication (estimated where dates not provided)	Patient withdrew consent or clinician's decision	Reason	Completed further follow-up

A2 Baseline data

Table T14 Baseline comparability of randomised groups

	Usual care + mirtazapine (n=xx)	Usual care + placebo (n=xx)	Total (n=xx)
Stratification variable: centre n(%)			
Bristol Exeter Manchester/Keele			

Hull/York			
Minimisation variables			
Female: n (%)			
Baseline BDI: n(%) 14-19 20-28 ≥29			
Currently receiving psychological services: n(%)			
Socio-demographic variables			
Age (years): mean (SD)			
Ethnic group, white: n(%)			
Marital status: n(%) Married/living as married Single Separated/widowed/divorced			
Employment status: n(%) In paid employment (full/part-time) Not in employment Unemployment due to ill health			
Educational attainment: n(%) A-level, higher grade or above GCSE, standard grade or above No formal qualifications			
Housing: n(%) Home owner Tenant or living with relative/friend Hostel/care home, homeless or other			
Financial well-being: n(%) Living comfortably/doing all right Just about getting by Finding it difficult/very difficult to make ends meet			
Alcohol consumption Audit score: median (IQR)			
Number of life events in the past 6 months: mean (SD)			
Social support score: mean (SD)			
Long-standing illness or disability; n(%) Any Diabetes Asthma or COPD Arthritis Heart disease or heart problems Stroke Cancer Kidney disease Mental health problems None of the above			
Caring responsibilities; n(%)			

Treatment preference			
Do you have a preference for either group?: n(%) Prefer to receive mirtazapine Prefer to receive the placebo Don't mind either way			
If you were to be allocated to the other group, how disappointed would you be?: n (%) Very Moderately A little bit Not really			
Measures of depression			
Suffered depression in the past: n (%)			
Family history of depression: n (%)			
Previous referral to a psychiatrist for depression: n (%)			
Number of prior episodes of depression: n (%) 0-1 2-4 ≥5			
Length of current course of anti-depressants: n(%) Less than 6 weeks 6 weeks – 3 months 3-6 months 6-12 months More than 12 months			
ICD-10 primary diagnosis: n(%) Mild Moderate Severe			
Secondary psychiatric diagnosis according to the CIS-R: n(%) *List according to responses*			
BDI-II score: mean (SD)			
GAD-7 score: mean (SD)			
PHQ-9 score: mean (SD)			
EQ-5D-5L score: mean (SD)			
SF-12 mental subscale: mean (SD)			
SF-12 physical subscale: mean (SD)			
CIS-R score: mean (SD)			
Suicidal ideation (CIS-R thoughts/plans): n (%)			

Note: Where data are incomplete for some variables, the numbers with information available are listed here

Table T15 Antidepressant medication use at baseline

		Usual care + mirtazapine (n=xx)		Usual care + placebo (n=xx)		Total (n=XXX)	
Antidepressant medication	**Dose (mg)**	**n**	**%**	**n**	**%**	**n**	**%**
List according to reported data							

Table T16 Summary of baseline variables related to missing BDI-II data at 12 weeks

	Missing (n=xx)	Present (n=xx)	p-value
Stratification variable: centre n(%)			
Bristol Exeter Manchester/Keele Hull/York			
Minimisation variables			
Female: n (%)			
Baseline BDI: n(%) 14-19 20-28 ≥29			
Currently receiving psychological services: n(%)			
Socio-demographic variables			
Age (years): mean (SD)			
Ethnic group, white: n(%)			
Marital status: n(%) Married/living as married Single Separated/widowed/divorced			
Employment status: n(%) In paid employment (full/part-time) Not in employment Unemployment due to ill health			
Educational attainment: n(%) A-level, higher grade or above GCSE, standard grade or above No formal qualifications			
Housing: n(%) Home owner Tenant or living with relative/friend Hostel/care home, homeless or other			
Financial well-being: n(%) Living comfortably/doing all right Just about getting by Finding it difficult/very difficult to make ends meet			
Alcohol consumption Audit score: median (IQR)			
Number of life events in the past 6 months: mean (SD)			
Social support score: mean (SD)			

Long-standing illness or disability; n(%) Any Diabetes Asthma or COPD Arthritis Heart disease or heart problems Stroke Cancer Kidney disease Mental health problems None of the above			
Caring responsibilities; n(%)			
Treatment preference			
Do you have a preference for either group?: n(%) Prefer to receive mirtazapine Prefer to receive the placebo Don't mind either way			
If you were to be allocated to the other group, how disappointed would you be?: n (%) Very Moderately A little bit Not really			
Measures of depression			
Suffered depression in the past: n (%)			
Family history of depression: n (%)			
Previous referral to a psychiatrist for depression: n (%)			
Number of prior episodes of depression: n (%) 0-1 2-4 ≥5			
Length of current course of anti-depressants: n(%) Less than 6 weeks 6 weeks – 3 months 3-6 months 6-12 months More than 12 months			
ICD-10 primary diagnosis: n(%) Mild Moderate Severe			
Secondary psychiatric diagnosis according to the CIS-R: n(%) *List according to responses*			
BDI-II score: mean (SD)			

GAD-7 score: mean (SD)			
PHQ-9 score: mean (SD)			
EQ-5D-5L score: mean (SD)			
SF-12 mental subscale: mean (SD)			
SF-12 physical subscale: mean (SD)			
CIS-R score: mean (SD)			
Suicidal ideation (CIS-R thoughts/plans): n (%)			

Table T17 Summary of baseline variables related to missing BDI-II data at 24 weeks

	Missing (n=xx)	Present (n=xx)	p-value
Stratification variable: centre n(%)			
Bristol Exeter Manchester/Keele Hull/York			
Minimisation variables			
Female: n (%)			
Baseline BDI: n(%) 14-19 20-28 ≥29			
Currently receiving psychological services: n(%)			
Socio-demographic variables			
Age (years): mean (SD)			
Ethnic group, white: n(%)			
Marital status: n(%) Married/living as married Single Separated/widowed/divorced			
Employment status: n(%) In paid employment (full/part-time) Not in employment Unemployment due to ill health			
Educational attainment: n(%) A-level, higher grade or above GCSE, standard grade or above No formal qualifications			
Housing: n(%) Home owner Tenant or living with relative/friend Hostel/care home, homeless or other			
Financial well-being: n(%) Living comfortably/doing all right Just about getting by Finding it difficult/very difficult to make ends meet			
Alcohol consumption Audit score: median (IQR)			

Number of life events in the past 6 months: mean (SD)			
Social support score: mean (SD)			
Long-standing illness or disability; n(%) Any Diabetes Asthma or COPD Arthritis Heart disease or heart problems Stroke Cancer Kidney disease Mental health problems None of the above			
Caring responsibilities; n(%)			
Treatment preference			
Do you have a preference for either group?: n(%) Prefer to receive mirtazapine Prefer to receive the placebo Don't mind either way			
If you were to be allocated to the other group, how disappointed would you be?: n (%) Very Moderately A little bit Not really			
Measures of depression			
Suffered depression in the past: n (%)			
Family history of depression: n (%)			
Previous referral to a psychiatrist for depression: n (%)			
Number of prior episodes of depression: n (%) 0-1 2-4 ≥5			
Length of current course of anti-depressants: n(%) Less than 6 weeks 6 weeks – 3 months 3-6 months 6-12 months More than 12 months			
ICD-10 primary diagnosis: n(%) Mild Moderate Severe			

Secondary psychiatric diagnosis according to the CIS-R: n(%) *List according to responses*			
BDI-II score: mean (SD)			
GAD-7 score: mean (SD)			
PHQ-9 score: mean (SD)			
EQ-5D-5L score: mean (SD)			
SF-12 mental subscale: mean (SD)			
SF-12 physical subscale: mean (SD)			
CIS-R score: mean (SD)			
Suicidal ideation (CIS-R thoughts/plans): n (%)			

Table T18 Summary of baseline variables related to missing BDI-II data at 12 months

	Missing (n=xx)	Present (n=xx)	p-value
Stratification variable: centre n(%)			
Bristol Exeter Manchester/Keele Hull/York			
Minimisation variables			
Female: n (%)			
Baseline BDI: n(%) 14-19 20-28 ≥29			
Currently receiving psychological services: n(%)			
Socio-demographic variables			
Age (years): mean (SD)			
Ethnic group, white: n(%)			
Marital status: n(%) Married/living as married Single Separated/widowed/divorced			
Employment status: n(%) In paid employment (full/part-time) Not in employment Unemployment due to ill health			
Educational attainment: n(%) A-level, higher grade or above GCSE, standard grade or above No formal qualifications			
Housing: n(%) Home owner Tenant or living with relative/friend Hostel/care home, homeless or other			
Financial well-being: n(%) Living comfortably/doing all right			

Just about getting by Finding it difficult/very difficult to make ends meet			
Alcohol consumption Audit score: median (IQR)			
Number of life events in the past 6 months: mean (SD)			
Social support score: mean (SD)			
Long-standing illness or disability; n(%) Any Diabetes Asthma or COPD Arthritis Heart disease or heart problems Stroke Cancer Kidney disease Mental health problems None of the above			
Caring responsibilities; n(%)			
Treatment preference			
Do you have a preference for either group?: n(%) Prefer to receive mirtazapine Prefer to receive the placebo Don't mind either way			
If you were to be allocated to the other group, how disappointed would you be?: n (%) Very Moderately A little bit Not really			
Measures of depression			
Suffered depression in the past: n (%)			
Family history of depression: n (%)			
Previous referral to a psychiatrist for depression: n (%)			
Number of prior episodes of depression: n (%) 0-1 2-4 ≥5			
Length of current course of anti-depressants: n(%) Less than 6 weeks 6 weeks – 3 months 3-6 months 6-12 months More than 12 months			

ICD-10 primary diagnosis: n(%) Mild Moderate Severe			
Secondary psychiatric diagnosis according to the CIS-R: n(%) *List according to responses*			
BDI-II score: mean (SD)			
GAD-7 score: mean (SD)			
PHQ-9 score: mean (SD)			
EQ-5D-5L score: mean (SD)			
SF-12 mental subscale: mean (SD)			
SF-12 physical subscale: mean (SD)			
CIS-R score: mean (SD)			
Suicidal ideation (CIS-R thoughts/plans): n (%)			

A3 Outcomes

Table T19 **Primary outcome: mean and difference in mean BDI-II scores at 12 weeks**

Randomisation groups	n	Mean	SD	Difference in means[a]	95% CI	p-value	Difference in means[b]	95% CI	p-value
Usual care + mirtazapine									
Usual care + placebo									
Total N									

[a] *ITT analysis adjusted for baseline BDI-II score and the stratification and other minimisation variables*
[b] *ITT analysis additionally adjusted for additional variables that show an imbalance between treatment groups at baseline*

Table T20 **Means and differences in mean BDI-II scores at 24 weeks and 12 months**

	Follow-up					
	24 weeks (n=)			12 months (n=)		
	n	Mean	SD	n	Mean	SD
Usual care + mirtazapine						
Usual care + placebo						

Regression analyses							
	N	Difference in means[a]	95% CI	p-value	Difference in means[b]	95% CI	p-value
24 weeks follow-up							
12 months follow-up							
Repeated measures							

[a] *ITT analysis adjusted for baseline BDI-II score and the stratification and other minimisation variables*
[b] *ITT analysis additionally adjusted for additional variables that show an imbalance between treatment groups at baseline*

Table T21 Percentage and OR of "response to treatment" (improvement of at least 50% in BDI-II score compared with baseline) at 12 weeks, 24 weeks and 12 months

	Follow-up								
	12 weeks (n=)			24 weeks (n=)			12 months (n=)		
	N	n	%[a]	N	n	%[a]	N	N	%[a]
Usual care + mirtazapine									
Usual care + placebo									

Regression analyses							
	N	OR[b]	95% CI	p-value	OR[c]	95% CI	p-value
12 weeks follow-up							
24 weeks follow-up							
12 months follow-up							
Repeated measures							

[a] *Number of patients reporting an improvement of at least 50% in BDI-II score compared with baseline (n) as a percentage of the total number (N) in the group*
[b] *ITT analysis adjusted for baseline BDI-II score and the stratification and other minimisation variables*
[c] *ITT analysis additionally adjusted for additional variables that show an imbalance between treatment groups at baseline*

Table T22 Percentage and OR of "remission of symptoms" (BDI-II of less than 10) at 12 weeks, 24 weeks and 12 months

	Follow-up								
	12 weeks (n=)			24 weeks (n=)			12 months (n=)		
	N	n	%[a]	N	N	%[a]	N	N	%[a]
Usual care + mirtazapine									
Usual care + placebo									

Regression analyses							
	N	OR[b]	95% CI	p-value	OR[c]	95% CI	p-value
12 weeks follow-up							
24 weeks follow-up							
12 months follow-up							
Repeated measures							

[a] *Number of patients reporting a BDI-II of less than 10 (n) as a percentage of the total number (N) in the group*
[b] *ITT analysis adjusted for baseline BDI-II score and the stratification and other minimisation variables*

[c] *ITT analysis additionally adjusted for additional variables that show an imbalance between treatment groups at baseline*

Table T23 **Means and differences in mean GAD-7 scores at 12 weeks, 24 weeks and 12 months**

	Follow-up								
	12 weeks (n=)			24 weeks (n=)			12 months (n=)		
	n	Mean	SD	n	Mean	SD	N	Mean	SD
Usual care + mirtazapine									
Usual care + placebo									
Regression analyses									
	N	Difference in means[a]	95% CI	p-value	Difference in means[b]	95% CI		p-value	
12 weeks follow-up									
24 weeks follow-up									
12 months follow-up									
Repeated measures									

[a] *ITT analysis adjusted for baseline GAD-7 score and the stratification and other minimisation variables*
[b] *ITT analysis additionally adjusted for additional variables that show an imbalance between treatment groups at baseline*

Table T24 **Percentage and OR of adherence at 12 weeks**

Randomisation groups	N	n	%[a]	OR[b]	95% CI	p-value	OR[c]	95% CI	p-value
Usual care + mirtazapine									
Usual care + placebo									
Total N									

[a] *Number of patients reported as being adherent as a percentage of the total number (N) in the group*
[b] *ITT analysis adjusted for the stratification and other minimisation variables*
[c] *ITT analysis additionally adjusted for additional variables that show an imbalance between treatment groups at baseline*

Table T25 **Means and differences in mean EQ-5D-5L scores at 12 weeks, 24 weeks and 12 months**

	Follow-up								
	12 weeks (n=)			24 weeks (n=)			12 months (n=)		
	n	Mean	SD	n	Mean	SD	N	Mean	SD
Usual care + mirtazapine									
Usual care + placebo									

Regression analyses									
	N	**Difference in means[a]**	**95% CI**	**p-value**	**N**	**Difference in means[b]**	**95% CI**	**p-value**
12 weeks follow-up								
24 weeks follow-up								
12 months follow-up								
Repeated measures								

[a] ITT analysis adjusted for baseline EQ-5D-5L score and the stratification and other minimisation variables
[b] ITT analysis additionally adjusted for additional variables that show an imbalance between treatment groups at baseline

Table T26 **Means and differences in mean ASEC scores at 12 weeks and 12 months**

	Follow-up					
	12 weeks (n=)			**12 months (n=)**		
	n	**Mean**	**SD**	**n**	**Mean**	**SD**
Usual care + mirtazapine						
Usual care + placebo						

Regression analyses							
	N	**Difference in means[a]**	**95% CI**	**p-value**	**Difference in means[b]**	**95% CI**	**p-value**
24 weeks follow-up							
12 months follow-up							
Repeated measures							

[a] ITT analysis adjusted for baseline ASEC score, stratification and other minimisation variables
[b] ITT analysis additionally adjusted for additional variables that show an imbalance between treatment groups at baseline

Table T27 **Comparison of results of ITT analysis of complete cases with ITT analysis where missing data were imputed using "best" and "worst" case scenarios and multiple imputation for primary outcome of BDI-II score at 12 weeks**

	n	**Difference in means[a]**	**95% CI**	**p-value**
Complete case				
"Best" case scenario				
"Worst" case scenario				
Multiple imputation				

[a] Adjusted for baseline BDI-II score, stratification and other minimisation variables and additional variables showing an imbalance between treatment groups at baseline

Table T28 Comparison of results from ITT, per protocol and CACE analyses for the primary outcome of BDI-II score at 12 weeks

	n	Difference in means[a]	95% CI	p-value
ITT				
Per protocol				
CACE				

[a] Adjusted for baseline BDI-II score, stratification and other minimisation variables and additional variables showing an imbalance between treatment groups at baseline

Table T29 Comparison of results from ITT and CACE analyses for the outcome of BDI-II score at 24 weeks

	n	Difference in means[a]	95% CI	p-value
ITT				
CACE (compliance at 12 weeks)				

[a] Adjusted for baseline BDI-II score, stratification and other minimisation variables and additional variables showing an imbalance between treatment groups at baseline

Table T30 Comparison of results from ITT, per protocol and CACE analyses for the outcome of BDI-II score at 12 months

	n	Difference in means[a]	95% CI	p-value
ITT				
Per protocol				
CACE (compliance at 12 weeks)				
CACE (compliance at 12 months)				

[a] Adjusted for baseline BDI-II score, stratification and other minimisation variables and additional variables showing an imbalance between treatment groups at baseline

Table T31 Comparison of results from ITT and CACE analyses for the outcome of improvement of at least 50% in BDI-II score at 12 weeks compared with baseline

	n	Regression coefficient[a]	95% CI	p-value
ITT				
CACE				

[a] Adjusted for baseline BDI-II score, stratification and other minimisation variables and additional variables showing an imbalance between treatment groups at baseline

Table T32 Comparison of results from ITT and CACE analyses for the outcome of improvement of at least 50% in BDI-II score at 24 weeks compared with baseline

	n	Regression coefficient[a]	95% CI	p-value
ITT				
CACE (compliance at 12 weeks)				

[a] Adjusted for baseline BDI-II score, stratification and other minimisation variables and additional variables showing an imbalance between treatment groups at baseline

Table T33 Comparison of results from ITT and CACE analyses for the outcome of improvement of at least 50% in BDI-II score at 12 months compared with baseline

	n	Regression coefficient[a]	95% CI	p-value
ITT				
CACE (compliance at 12 weeks)				
CACE (compliance at 12 months)				

[a] *Adjusted for baseline BDI-II score, stratification and other minimisation variables and additional variables showing an imbalance between treatment groups at baseline*

Table T34 Comparison of results from ITT and CACE analyses for the outcome of remission of symptoms defined by a BDI-II score of less than 10 at 12 weeks

	n	Regression coefficient[a]	95% CI	p-value
ITT				
CACE (compliance at 12 weeks)				

[a] *Adjusted for baseline BDI-II score, stratification and other minimisation variables and additional variables showing an imbalance between treatment groups at baseline*

Table T35 Comparison of results from ITT and CACE analyses for the outcome of remission of symptoms defined by a BDI-II score of less than 10 at 24 weeks

	n	Regression coefficient[a]	95% CI	p-value
ITT				
CACE (compliance at 12 weeks)				

[a] *Adjusted for baseline BDI-II score, stratification and other minimisation variables and additional variables showing an imbalance between treatment groups at baseline*

Table T36 Comparison of results from ITT and CACE analyses for the outcome of remission of symptoms defined by a BDI-II score of less than 10 at 12 months

	n	Regression coefficient[a]	95% CI	p-value
ITT				
CACE (compliance at 12 weeks)				
CACE (compliance at 12 months)				

[a] *Adjusted for baseline BDI-II score, stratification and other minimisation variables and additional variables showing an imbalance between treatment groups at baseline*

A.4 Safety data

Table T37 Expected adverse events and serious adverse events

	Received usual care + mirtazapine						Received usual care + placebo					
	Events		Patients (n=XX)				Events		Patients (n=XX)			
	AE	SAE	AE	%	SAE	%	AE	SAE	AE	%	SAE	%
PATIENTS WITH ≥1 EVENT												
Metabolic												
Increase in appetite												
Weight increased												
Hypnotraemia												
Gastrointestinal disorders												
Dry mouth												
Nausea												
Diarrhoea												
Vomiting												
Oral hypoaesthesia												
Pancreatitis												
Mouth oedema												
Increased salivation												
Nervous system												
Somnolence												
Sedation												
Headache												
Lethargy												
Dizziness												
Tremor												

	Received usual care + mirtazapine						Received usual care + placebo					
	Events		Patients (n=XX)				Events		Patients (n=XX)			
	AE	SAE	AE	%	SAE	%	AE	SAE	AE	%	SAE	%
Paraesthesiae												
Restless legs												
Syncope												
Myoclonus												
Convulsions												
Serotonin Syndrome												
Oral paraesthesia												
Dysarthria												
Psychiatric disorders												
Abnormal dreams												
Confusion												
Anxiety												
Insomnia												
Nightmares												
Mania												
Agitation												
Hallucinations												
Psychomotor restlessness												
Aggression												
Suicidal ideation												
Suicidal behaviour												
Muscoskeletal disorders												
Back pain												
Arthralgia												

	Received usual care + mirtazapine						Received usual care + placebo					
	Events		Patients (n=XX)				Events		Patients (n=XX)			
	AE	SAE	AE	%	SAE	%	AE	SAE	AE	%	SAE	%
Myalgia *Rhabdomyolysis*												
Vascular disorders *Orthostatic hypotension* *Hypotension*												
Blood and lymphatics *Bone marrow depression* *Eosinophilia*												
Hepato-biliary disorders *Elevation in serum transaminase*												
General disorders and administration site conditions *Peripheral oedema* *Fatigue* *Somnambulism*												
Skin and subcutaneous tissue disorders *Exanthema* *Stevens-Johnson syndrome* *Dermatitis bullous* *Erythema multiforme* *Toxic epidermal necrolytis*												
Renal and urinary disorders *Urinary retention*												

	Received usual care + mirtazapine						Received usual care + placebo					
	Events		Patients (n=XX)				Events		Patients (n=XX)			
	AE	SAE	AE	%	SAE	%	AE	SAE	AE	%	SAE	%
Endocrine disorders *Inappropriate antidiuretic hormone secretion*												
Other symptoms, side effects or adverse event listed in the Summary of Product Characteristics and BNF *Listed as observed*												

Notes: *SAEs are a subset of AEs.*

Table T38 **Expected adverse events and serious adverse events by relatedness to treatment (UR: un-related; RL: related)**

	Received usual care + mirtazapine												Received usual care + placebo											
	Events				Patients (n=XX)								Events				Patients (n=XX)							
	AE		SAE		AE				SAE				AE		SAE		AE				SAE			
	UR	RL	UR	RL	UR	%	RL	%	UR	%	RL	%	UR	RL	UR	RL	UR	%	RL	%	UR	%	RL	%
PATIENTS WITH ≥1 EVENT																								
Metabolic *Increase in appetite* *Weight increased* *Hypnotraemia*																								
Gastrointestinal disorders *Dry mouth* *Nausea* *Diarrhoea*																								

	Received usual care + mirtazapine												Received usual care + placebo											
	Events				Patients (n=XX)								Events				Patients (n=XX)							
	AE		SAE		AE				SAE				AE		SAE		AE				SAE			
	UR	RL	UR	RL	UR	%	RL	%	UR	%	RL	%	UR	RL	UR	RL	UR	%	RL	%	UR	%	RL	%
Vomiting																								
Oral hypoaesthesia																								
Pancreatitis																								
Mouth oedema																								
Increased salivation																								
Nervous system																								
Somnolence																								
Sedation																								
Headache																								
Lethargy																								
Dizziness																								
Tremor																								
Paraesthesiae																								
Restless legs																								
Syncope																								
Myoclonus																								
Convulsions																								
Serotonin Syndrome																								
Oral paraesthesia																								
Dysarthria																								
Psychiatric disorders																								
Abnormal dreams																								
Confusion																								
Anxiety																								

	Received usual care + mirtazapine												Received usual care + placebo											
	Events				Patients (n=XX)								Events				Patients (n=XX)							
	AE		SAE		AE				SAE				AE		SAE		AE				SAE			
	UR	RL	UR	RL	UR	%	RL	%	UR	%	RL	%	UR	RL	UR	RL	UR	%	RL	%	UR	%	RL	%
Insomnia																								
Nightmares																								
Mania																								
Agitation																								
Hallucinations																								
Psychomotor restlessness																								
Aggression																								
Suicidal ideation																								
Suicidal behaviour																								
Muscoskeletal disorders																								
Back pain																								
Arthralgia																								
Myalgia																								
Rhabdomyolysis																								
Vascular disorders																								
Orthostatic hypotension																								
Hypotension																								
Blood and lymphatics																								
Bone marrow depression																								

	Received usual care + mirtazapine												Received usual care + placebo											
	Events				Patients (n=XX)								Events				Patients (n=XX)							
	AE		SAE		AE				SAE				AE		SAE		AE				SAE			
	UR	RL	UR	RL	UR	%	RL	%	UR	%	RL	%	UR	RL	UR	RL	UR	%	RL	%	UR	%	RL	%
Eosinophilia																								
Hepato-biliary disorders *Elevation in serum transaminase*																								
General disorders and administration site conditions *Peripheral oedema* *Fatigue* *Somnambulism*																								
Skin and subcutaneous tissue disorders *Exanthema* *Stevens-Johnson syndrome* *Dermatitis bullous* *Erythema multiforme* *Toxic epidermal necrolytis*																								
Renal and urinary disorders *Urinary retention*																								
Endocrine disorders																								

	Received usual care + mirtazapine												Received usual care + placebo											
	Events				Patients (n=XX)								Events				Patients (n=XX)							
	AE		SAE		AE				SAE				AE		SAE		AE				SAE			
	UR	RL	UR	RL	UR	%	RL	%	UR	%	RL	%	UR	RL	UR	RL	UR	%	RL	%	UR	%	RL	%
Inappropriate antidiuretic hormone secretion																								
Other symptoms, side effects or adverse event listed in the Summary of Product Characteristics and BNF *Listed as observed*																								

Notes: *SAEs are a subset of AEs.*

Table T39 Unexpected adverse events and serious adverse events

		Received usual care + mirtazapine (n=XX)		Received usual care + placebo (n=XX)	
		n	%	N	%
Number of patients experiencing one or more SAEs					
Number of events					
Reason event classified as SAE	Resulted in death				
	Is/was life threatening				
	Resulted in persistent or significant disability/incapacity				
	Prolonged ongoing hospitalisation/ caused hospitalisation (other than hospitalisations for social reasons in absence of an adverse event, in-clinic protocol measures and surgery/procedure planned before entry into the trial)				
	Other				
Relatedness to *treatment*	Not related				
	Unlikely to be related				
	Possibly related				
	Probably related				
	Definitely related				

Table T40 Details of serious unexpected adverse events

Study ID=	Treatment randomised to=	Treatment received=	Patient withdrawn from study (and when)=
Treatment start date=	Timing of SAE in terms of starting study medication =		
Brief description of event=	Location=	Maximum intensity=	Relatedness=
SAE start date=	SAE resolution date=	Event resulted in death=	Event was life threatening=
Event resulted in persistent/significant disability/incapacity=	Event prolonged ongoing hospitalisation/resulted in hospitalisation=	Other reason for reporting as SAE (with details)=	

Table T41 Number of adverse events per patient stratified by relatedness to treatment

	Received usual care + mirtazapine (n=XX)						Received usual care + placebo (n=XX)					
	All		Un-related		Related		All		Un-related		Related	
	n	%	n	%	n	%	n	%	n	%	n	%
0												
1												
2												
3												
4+												

Total						

APPENDIX B: SUMMARY OF DATA COLLECTED AT EACH TIME POINT

CONCEPT	MEASURE	TIME POINT					
		SCREENING QUESTIONNAIRE	BASELINE	6 WEEKS	12 WEEKS	24 WEEKS	12 MONTHS
CONSENT			X				
SOCIO-DEMOGRAPHICS		X	X				
VIEWS ON TREATMENT			X				
ASSESSMENT OF BLINDING					X		
CURRENT MEDICATION USE		X					
DEPRESSION SEVERITY	BDI-II	X	X	X	X	X	X
ADHERENCE	4-ITEM MORISKY (ADAPTED)	X	X	X	X	X	X
ANXIETY	GAD-7		X		X	X	X
DEPRESSION SEVERITY	PHQ9		X		X	X	X
QUALITY OF LIFE	EQ-5D-5L		X		X	X	X
QUALITY OF LIFE	SF-12		X		X	X	X
ICD-10 DIAGNOSIS	CIS-R		X				
ANTIDEPRESSANT SIDE-EFFECTS	ASEC		X		X		X
USE OF TRIAL MEDICATION				X	X	X	X
USE OF USUAL MEDICATION				X	X	X	X
HEALTH EVENTS (SAES)				X	X	X	X
USE OF HEALTH AND SOCIAL SERVICES	BESPOKE QUESTIONNAIRE				X	X	X
EXIT QUESTIONNAIRE							X

APPENDIX C: ECONOMIC EVALUATION ANALYSES

Economic evaluation

Aim

The economic evaluation will assess the cost-effectiveness of mirtazapine plus SSRI or SNRI compared with SSRI or SNRI alone, for primary care patients with TRD. We will do this by valuing the relative costs and benefits of the combined therapy compared with SSRI or SNRI alone.

Background

Mirtazapine is inexpensive and is a well-established treatment for depression. Therefore if it is clinically effective as an additional treatment in this group of treatment resistant patients it is likely to be cost-effective. However, differential resource use between the 2 arms during the follow-up is a possibility, perhaps associated with the potential for adverse reactions. This would make the intervention more expensive than it might first appear.

It has been shown elsewhere that direct and indirect costs for people with TRD are substantially higher than for major depressive disorder controls. Findings from the economic analysis should therefore be of value to NICE and to commissioners in estimating the initial affordability of treating TRD with mirtazapine and the probability of future savings.

We also think it is important to have an accurate estimate of cost per QALY of various treatment options for TRD. We have cost-effectiveness estimates for the use of cognitive behavioural therapy in TRD from the CoBalT trial. By collecting economic data in this trial we will be able to estimate the relative cost-effectiveness of mirtazapine versus other treatment options such as CBT.

Perspective

The two treatment strategies will be compared from the viewpoint of: (i) the NHS and personal social services (PSS); (ii) patients and carers; and (iii) society. The analysis will be based on the costs incurred by the health service providers, patients and care-givers, and societal costa of time off work at 12 weeks and 12 months after randomisation into each group.

Prior relevant work

Whilst there has been considerable work around calculating unit costs, there is little empirical data to inform the method of economic data collection. In the CoBalT trial, we collected data on health service utilisation using a self-report questionnaire and also gathered data from primary care records. We will use both of these methods to estimate resource use. As primary care consultations are mainly with a non-specialist and it is often difficult to identify a precise reason for the encounter, we will include all such consultations regardless of whether they are clearly related to depression. For secondary care costs, we will initial include "all cause" resource use, but will conduct a sensitivity analysis excluding resource use (for example, orthopaedic interventions) judge unlikely to be related to depression.

Data collection

This is informed by the CoBalT study described above. Data on resource use will be collected from two main sources:

1. Practice records will provide information on: number of primary care consultations, by type (for example, face-to-face, telephone, etc.) and who seen; and prescribed medication.
2. A questionnaire, administered at 12 and 24 weeks and 12 months, will provide information on: use of other primary and community care services (NHS Direct, attendances at walk-in centres, use of community health care services); secondary care related to mental health (number of out-patient visits, type of clinic, and reason for visit; inpatient stays, length of stay and reason); use of social services and disability payments received; personal costs related to mental health (expenditure on over-the-counter medication, expenditure on prescriptions, travel costs associated with health care visits, loss of earnings, out of pocket expenditure on other services, such as private counselling or complementary and alternative therapies, child care and domestic help); time off work and unpaid activities.

The principle of opportunity cost will underlie the valuation of resource use though in many cases market prices will act as a proxy. The intervention will be valued using the mid-point salaries of staff and the cost of overheads. Recognised published sources will be used to value service use: Curtis and Netten (http://www.pssru.ac.uk/uc/uc2011contents.htm) for primary and community care consultations and the use of social servies; national evaluations for consultations with NHS Direct and walk-in centres (http://www.shef.ac.uk/content/1/c6/02/40/50/nhsd3.pdf), DH tariff for A&E, OP and inpatient episodes (http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_123459), and the British National Formulary (http://www.bnf.org/bnf) for prescribed medication. Time off work by patients and care-givers will be valued using the friction approach, which includes only the resources required to replace the employee.

We will conduct the following: a cost-effectiveness analysis relating the costs of each strategy to the change in BDI-II scores at 12 weeks; a cost-effectiveness analysis relating the costs of each strategy to the change in depression scores at 12 months; a cost-utility analysis relating the costs of each strategy to QALYs gained, using the EQ-5D-5L at 12 months; and a cost consequences study relating the costs of each strategy from each perspective to changes in a portfolio of outcomes at 12 months.

Discounting will not be necessary, as the costs and outcomes will cover a period of one year only.

The effect of uncertainty in unit costs estimates or assumptions about resource use will be addressed in sensitivity analyses. Uncertainty in the cost-effectiveness/utility ratios resulting from patient variation in resource use and effectiveness will be captured by estimating confidence intervals around the net benefit statistic and estimating cost-effectiveness acceptability curves.

APPENDIX D: QUALITATIVE ANALYSES

Aim

The aim of this study is to: (i) explore patients' views and experiences of taking either two antidepressant medications or an antidepressant and a placebo; (ii) identify patients' reasons for completing or not completing the study, including withdrawal from study medication; and (iii) explore the views of general practitioners on prescribing a second antidepressant in this patient group.

Background

We acknowledge that it is unusual to have a qualitative component in a pharmacological trial; we think this is a strength rather than a weakness and will provide valuable information for implementation in clinical practice. It allows us to explore certain areas in more depth than would otherwise be possible. We are testing a new combination of drugs rather than a new drug, and the attitude of both GPs to prescribing and patients to taking two antidepressants s of considerable importance. We do not know what patient attitudes to taking two antidepressants are; there may considerable resistance. We do know that older people (who may be more likely to have depression that does not

respond to an SSRI) can be reluctant to take antidepressants. Up until new, combination antidepressant treatment has been mainly the preserve of psychiatrists and the NICE guidance (Depression CG90) supports this, GP attitudes to the addition of a second antidepressant are also relevant. If the intervention is effective and cost effective it will be particularly useful to have a better understanding of the potential barriers and facilitators to implementing combination antidepressant therapy as routine practice in primary care, and qualitative work will help us gain this understanding.

Recruitment and sampling

At the baseline assessment for the main study, individuals will be informed about the qualitative element of the trial and asked to consent to the possibility of being contacted by the qualitative research team to take part in an interview.

A purposeful sampling strategy will be used to identify potential interviewees to ensure interviews are held with participants in both arms of the trial, and with individuals in both arms who vary in their levels of adherence. Within this purposeful strategy, maximum variation sampling techniques will be used so that patients of different socio-economic background, gender and age are invited for interview. Patients will be sampled across the four centres.

Interviews will be held with patients after the primary outcome measure has been obtained (at 12 weeks post-randomisation) to avoid the possibility of bias that might be introduced by the qualitative interview having a supportive role. Individuals will be interviewed within 8 weeks of their primary outcome measures being taken.